An Improved Method for the Synthesis of Active Esters of *N*-Protected Amino Acids and Subsequent Synthesis of Dipeptides

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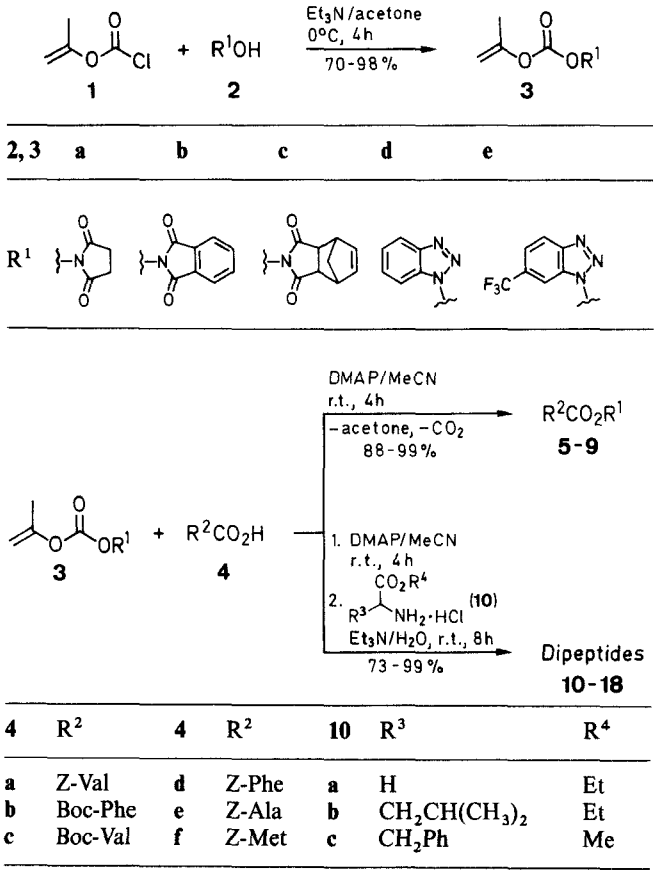
4-Dimethylaminopyridine-catalyzed reaction of mixed carbonates **3** with *N*-protected amino acids **4** gave the corresponding active esters **5–9**, from which dipeptides **11–18** were synthesized by aminolysis with amino acids **10**.

Active esters of *N*-protected amino acids have been widely used as versatile synthetic intermediates, especially in peptide synthesis, and several methods for the formation of a variety of active esters have been studied extensively.[1] As part of a continuing research program on the preparation of active esters, we have reported on the use of condensing agents such as carbonates,[2] oxalates,[3] and dithiocarbonates,[4] having active ester groups which could be successfully employed in the peptide or ester syntheses. Recently, Jaouadi et al.[5] reported on syntheses of the activated esters of Boc-amino acids using mixed isopropenyl carbonates (aryl/isopropenyl and isopropenyl/*N*-succinimidyl) in the presence of a stoichiometric amount of *N*-methylmorpholine (NMM). However, the yields of the activated esters using the above reagents, especially those of *N*-hydroxysuccinimide esters, were not so high (49–76%). Furthermore, data required for the characterization of the products, e.g. specific rotations and melting points were not given.

In this paper, we wish to report the synthesis of the active esters of *N*-protected amino acids using the carbonate **3a–e** and a catalytic amount of 4-dimethylaminopyridine (DMAP),[6] and their aminolysis to dipeptides **11–18**. The reagents **3a–e** could easily be prepared from isopropenyl chloroformate and the corresponding *N*-hydroxy compounds in the presence of triethylamine (Scheme). These reagents are stable at room temperature and easy to handle (Table 1). Only a catalytic amount of DMAP is enough to effect the reaction shown in the Scheme, and the reaction of *N*-protected amino acids **4** with **3a–e** was clean compared to that involving NMM.[5] The reaction proceeded smoothly in acetonitrile or dioxane at room temperature and the operation is very simple. Moreover a one-pot dipeptide synthesis was feasible to give the products as shown in the Scheme. The resulting active esters **5–9** and dipeptides **11–18** appeared as a single spot on TLC, after the usual aqueous workup. All products were obtained in good yield and gave virtually the same specific rotation as reported and high yields (Table 2).



4	R^2	4	R^2	10	R^3	R^4
a	Z-Val	d	Z-Phe	a	H	Et
b	Boc-Phe	e	Z-Ala	b	$CH_2CH(CH_3)_2$	Et
c	Boc-Val	f	Z-Met	c	CH_2Ph	Me

Scheme

Table 1. Mixed Carbonates **3a–e** Prepared

Product	Yield (%)	mp (°C) (solvent)	Molecular Formula[a] or Lit. mp (°C)	IR ($CHCl_3$) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)	MS m/z (M^+)
3a	96	106–110 (Et_2O/hexane)	99–101[5]	3000, 2900, 1800[b]	2.02 (s, 3H), 2.81 (s, 4H), 4.80 (m, 1H), 5.00 (d, 1H, J = 3.0)	199
3b	95	120–122 (Et_2O/hexane)	$C_{12}H_9NO_5$ (247.2)	3025, 1820, 1790, 1750	2.07 (s, 3H), 4.83 (m, 1H), 5.03 (d, 1H, J = 3.0), 7.78–8.03 (m, 4H)	247
3c	98	117–120 (Et_2O/hexane)	$C_{13}H_{13}NO_5$ (263.2)	2950, 1820, 1740, 1685	1.53 (d, 1H, J = 9.0), 1.79 (dt, 1H, J = 1.5, 9.0), 2.00 (s, 3H), 3.32 (dd, 1H, J = 1.5, 3.0), 3.47 (m, 1H), 4.79 (dd, 1H, J = 1.0, 3.0), 4.96 (d, 1H, J = 3.0), 6.19 (m, 2H)	263
3d	70	151–153 (acetone/Et_2O)	$C_{10}H_9N_3O_3$ (219.2)	2975, 1765	2.17 (s, 3H), 4.98 (m, 1H), 5.05 (d, 1H, J = 3.0), 7.50–8.30 (m, 4H)	219
3e	83	164–166 (acetone/i-Pr_2O)	$C_{11}H_8F_3N_3O_3$ (287.2)	3030, 1790	2.18 (s, 3H), 4.98 (m, 1H), 5.09 (d, 1H, J = 3.0), 7.98–8.45 (m, 3H)	287

[a] Satisfactory microanalyses obtained: C, H, N ±0.17. [b] KBr pellet.

Table 2. Compounds **5–9**, **11–18** Prepared

Entry	Reaction Conditions			Product[a]	Yield (%)	mp (°C)	Molecular Formula[b] or Lit. mp (°C)	$[\alpha]_D$ (°C, *c*, solvent)[c]	
	Mixed Carbonate	Amino Acid or Amino Acid + **10**	solvent					found	reported
1	**3a**	**4a**	MeCN	Z-Val-OSu (**5**)	99	119–121	116–117[7]	−25.3 (27, 2, D)	−25.1[7] (25, 2, D)
2			dioxane	**5**	92	118–120		−25.1 (28, 2, D)	
3			MeCN	**5**	94[d]	118–120		−24.4 (23, 2, D)	
4	**3a**	**4b**	MeCN	Boc-Phe-OSu (**6**)	88	156–157	152–153[7]	−18.8 (26, 2, D)	−19.0[7] (25, 2, D)
5			dioxane	**6**	96	155–156		−19.5 (26, 2, D)	
6	**3a**	**4c**	dioxane	Boc-Val-OSu (**7**)	99	133–134	128–129[7]	−40.7 (24, 2, D)	−37.0[7] (25, 2, D)
7	**3b**	**4a**	dioxane	Z-Val-OPht (**8**)	96	141–142	$C_{21}H_{20}N_2O_6$ (396.4)	−31.9 (26, 2, D)	–
8	**3c**	**4a**	MeCN	Z-Val-ONb (**9**)	99	92–94	99–101[11]	−25.5 (25, 2, D)	−25.2[11] (22, 2, D)
9	**3a**	**4d** + **10b**	MeCN	Z-Phe-Leu-OEt (**11**)	99	120–121	116–118[8]	−24.2 (28, 2, E)	−23.0[8] (26, 2, E)
10	**3a**	**4a** + **10b**	MeCN	Z-Val-Leu-OEt (**12**)	99	104–105	103–105[9]	−45.9 (25, 2, E)	−42.0[9] (24, 2, E)
11	**3b**	**4d** + **10a**	dioxane	Z-Phe-Gly-OEt (**13**)	73	113–115	109–111[10]	−16.5 (24, 2, E)	−17.0[10] (20, 1, E)
12	**3c**	**4a** + **10a**	MeCN	Z-Val-Gly-OEt (**14**)	98	172–173	169–170[9]	−6.1 (27, 1, EA)	−6.0[9] (24, 1, EA)
13	**3d**	**4f** + **10b**	MeCN	Z-Met-Leu-OEt (**15**)	90	73–76	78–79[8]	−28.3 (26, 1, E)	−29.2[8] (24, 1, E)
14	**3d**	**4d** + **10c**	dioxane	Z-Phe-Phe-OMe (**16**)	80	152	146–148[12]	−20.2 (29, 1, M)	−20.0[13] (25, 0.26, M)
15	**3e**	**4e** + **10a**	dioxane	Z-Ala-Gly-OEt (**17**)	79	102–103	99–101[10]	−21.6 (26, 2, E)	−22.2[10] (20, 1, E)
16	**3e**	**4e** + **10c**	dioxane	Z-Ala-Phe-OMe (**18**)	74	106–107	98–99[14]	−14.1 (29, 2, M)	−14[14] (M)

[a] All products were characterized by their IR, ^{1}H-NMR and mass spectra. Su = succinimide, Pht = phthalimide, Nb = norbornenylsuccinimide.
[b] Satisfactory microanalyses obtained: C, H, N ±0.3.
[c] D = dioxane, E = EtOH, EA = EtOAc, M = MeOH.
[d] DMAP on polystyrene (1.6 mmol/g resin, Fluka) as catalyst (0.33 g, 0.5 mmol) was used.

Change of solvent from acetonitrile to dioxane made no difference in the yields and $[\alpha]_D$ (entries 1, 2 and 4, 5). Furthermore, the use of "DMAP on polystyrene" instead of DMAP as the catalyst, also led to the formation of satisfactory product judging from yield and purity of the product (entry 3). Generally, racemization is apt to be effected with the excess base used for the generation of carboxylate ion, and aminolysis by amino acid hydrochloride. In the active esterification step involving these reagents, the possibility of racemization may be negligible because of the use of only a catalytic amount of base.

In conclusion, the present reaction is an improved method for the synthesis of active esters starting from isopropenyl carbonates **1** and *N*-protected amino acids **4** in the presence of a catalytic amount of DMAP under mild conditions.

IR spectra were recorded on a Hitachi 260-30 spectrophotometer, ^{1}H-NMR spectra on Varian EM-390 (90 MHz) or Varian VXR-300 (300 MHz) spectrometers and mass spectra on a Jeol JMS-DX-300 mass spectrometer. Optical rotations were measured using a Jasco model DIP-181 polarimeter.

Isopropenyl Succinimido Carbonate (3a); Typical Procedure:
A solution of isopropenyl chloroformate (**1**; 1.32 g, 11 mmol) in MeCN (10 mL) is added to a stirred solution of *N*-hydroxysuccinimide (**2a**; 1.15 g, 10 mmol) and Et_3N (1.11 g, 11 mmol) in acetone (150 mL) at 0 °C. After 4 h, the $Et_3N \cdot HCl$ formed is removed by filtration and the solvent evaporated under reduced pressure. EtOAc (150 mL) is added to the residue, and the EtOAc solution is washed with 1 N HCl (100 mL), H_2O (100 mL), 4% $NaHCO_3$ (100 mL), and brine (100 mL). The organic phase is dried (Na_2SO_4), evaporated, and the residue is recrystallized to give **3a**; yield: 1.91 g (96%) (Table 1).

Protected Amino Acid Active Esters 5–9; General Procedure:
A mixture of *N*-protected amino acid **4** (0.5 mmol), carbonate **3** (0.5 mmol), and DMAP (6.1 mg, 0.05 mmol) in MeCN (3 mL) is stirred for 4 h at r.t. The solvent is removed *in vacuo*, the residue dissolved in EtOAc (100 mL) and the organic solution is washed successively with 1 N HCl (50 mL), H_2O (50 mL), 5% $NaHCO_3$ (50 mL), brine (50 mL) and dried (Na_2SO_4). The solvent is evaporated and the product is purified by recrystallization (Table 2).

Protected Dipeptide Esters 11–18; General Procedure:
A mixture of appropriate *N*-protected amino acid **5–9** (0.5 mmol), carbonate **3** (0.5 mmol), and DMAP (6.1 mg, 0.05 mmol) in MeCN (3 mL) is stirred for 4 h at r.t., then the amino acid ester hydrochloride **10** (0.5 mmol) and Et_3N (0.5 mmol) in H_2O (1 mL) are added and is stirred for 8 h at r.t. After removal of the solvent *in vacuo*, the residue is dissolved in EtOAc (100 mL) and the organic solution is washed successively with 1 N HCl (50 mL), H_2O (50 mL), 5% $NaHCO_3$ (50 mL), brine (50 mL) and dried (Na_2SO_4). After evaporation of EtOAc, the product is purified by recrystallization (Table 2).

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(1) Gross, E.; Meienhofer, J. *The Peptides, Analysis, Synthesis, Biology*, Vol. 1, Academic Press, New York, 1979, and references cited therein.
(2) Ogura, H.; Kobayashi, K.; Shimizu, K.; Kawabe, K.; Takeda, K. *Tetrahedron Lett.* **1979**, 4745.
(3) Takeda, K.; Sawada, I.; Suzuki, A.; Ogura, H. *Tetrahedron Lett.* **1983**, *24*, 4451.
Takeda, K.; Tsuboyama, K.; Yamaguchi, K.; Ogura, H. *J. Org. Chem.* **1985**, *50*, 273.
(4) Takeda, K.; Tsuboyama, K.; Takayanagi, H.; Ogura, H. *Synthesis* **1987**, 557.
(5) Jaouadi, M.; Selve, C.; Dormoy, J.R.; Castro, B.; Martinez, J. *Tetrahedron Lett.* **1985**, 1721.
(6) For recent applications of DMAP for the esterification of carboxylic acids, see:
Kim, S.; Kim, Y.C.; Lee, J.I. *Tetrahedron Lett.* **1983**, *24*, 3365.
Kim, S.; Lee, J.I. *J. Org. Chem.* **1983**, *48*, 2608.
Kim, S.; Lee, J.I.; Ko, Y.K. *Tetrahedron Lett.* **1984**, *25*, 4943.
Jaouadi, M.; Selve, C.; Dormoy, J.R.; Castro, B. *Bull. Soc. Chim. Fr.* **1984**, 409.
Kim, S.; Lee, J.I.; Kim, Y.C. *J. Org. Chem.* **1985**, *50*, 560.
Kim, S.; Ko, Y.K. *J. Chem. Soc., Chem. Commun.* **1985**, *473*.
Jouin, P.; Castro, B.; Zeggaf, C.; Pantaloni, A.; Senet, J.P.; Lecolier, S.; Sennyey, G. *Tetrahedron Lett.* **1987**, *28*, 1661.
Jouin, P.; Castro, B.; Zeggaf, C.; Pantaloni, A.; Senet, J.P.; Lecolier, S.; Sennyey, G. *Tetrahedron Lett.* **1987**, *28*, 1665.
(7) Anderson, G.; Zimmerman, J.E.; Callahan, F.M. *J. Am. Chem. Soc.* **1964**, *86*, 1839.
(8) Ogura, H.; Takeda, K. *Nippon Kagaku Kaishi* **1981**, 836; *C.A.* **1981**, *95*, 187635.
(9) Bergel, F.; Stock, J.A. *J. Chem. Soc.* **1960**, 3658.
(10) Miyoshi, M. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1489.
(11) Fujino, M.; Kobayashi, S.; Obayashi, M.; Fukuda, T.; Shinagawa, S.; Nishimura, O. *Chem. Pharm. Bull.* **1974**, *22*, 1857.
(12) Katsoyannis, P.G.; Ginos, J.; Schwartz, G.P.; Cosmatos, A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1311.
(13) Tilak, M.A.; Hoffmann, J.A. *J. Org. Chem.* **1977**, *42*, 2098.
(14) Borin, G.; Marchiori, M.; Moroder, L.; Scoffone, E. *Gazz. Chem. Ital.* **1975**, *105*, 137.

Errata and Addenda

1990

Chang, Y.-H.; Uang, B.-J.; Wu, C.-M.; Yu, T.-H.
Synthesis **1990**, 1033. The correct country in the address of the Authors on page 1033 in both cases should be, Taiwan, Republic of China.

1991

Marchand, A. P.; Reddy, G. M. *Synthesis* **1991**, 198.
The following correction was received from Professor Marchand. Shortly after the appearance of our paper, we became aware of a comparable study of ultrasonic acceleration of the reduction of polycyclic 1,2-dicarbonylethylene and 1,2-dicarbonylcyclobutane derivatives with zinc/acetic acid (Chou, T.-C.; Hong, F.-T.; Chuang, K.-S. *Tunghai J.* **1987**, *28*, 659). We thank Professor Teh-Chang Chou of having brought this paper to our attention.

Lesher, G. Y.; Singh, B. *Synthesis* **1991**, 211.
Note the correct spelling of Dr. Singh's forename is Baldev.

Takeda, K.; Ayabe, A.; Suzuki, M.; Konda, Y.; Harigaya, Y. *Synthesis* **1991**, 689. In footnote d of Table 2 on page 690 the correct quantity of 4-dimethylaminopyridine (DMAP) should be 0.033g, 0.05 mmol.